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*Case Report*

# Primary intrahepatic bile duct adenocarcinoma complicating with nonalcoholic fatty liver disease in an elderly woman: independent risk factor or a mere coincidence? A case report

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**Abstract:** Our report detailes an eldly woman with multiple liver space-occupying lesions (SOLs). Abdominal ultrasonography revealed multiple hypoechoic masses of different sizes, and enhanced computed tomography showed multiple nodules and masses in the liver parenchyma. Ultrasound-guided liver biopsy was performed because the radiological and endoscopic examinations could not determine the diagnosis. Pathological diagnosis indicated poorly differentiated adenocarcinoma. Immunohistochemical staining showed that the expression of CK7, CK8/18, CK19, mammaglobin, ER/SP1, PR/1E2 and GS were positive whereas the expression of Hepatocyte, AFP, GPC-3, WT-1, CK20, CD34, Syn, CgA, CD56, TTF-1, NapsinA, CDX-2, GCDFP 15 and CA125 were negative. Combined with pathological and immunohistochemical results, the diagnosis was determined as the primary intrahepatic bile duct adenocarcinoma. However, no definite risk factor had been found for this patient, and we found that the patient had a medical history of fatty liver for 20 years. She was obese, with a body weight of 92 kilograms (BMI, 32.86 $Kg/m^2$), and radiological examinations showed the typical imaging characteristics for fatty liver. According to our current knowledge, we deduce that nonalcoholic fatty liver disease may be the possible risk factor for this patient with intrahepatic bile duct adenocarcinoma, but a mere coincidence cannot be ruled out. In this report, we detail the case and discuss the relationship between nonalcoholic fatty liver disease and primary intrahepatic bile duct adenocarcinoma.

**Keywords:** Intrahepatic bile duct adenocarcinoma, nonalcoholic fatty liver disease, risk factor, intrahepatic cholangiocarcinoma

## Introduction

Liver space-occupying lesions (SOLs) can be caused by various diseases, including malignant lesions, such as hepatocellular carcinoma, cholangiocarcinoma (bile duct cancer or carcinoma) and metastatic tumors, and benign lesions, such as hepatic hemangioma, hepatic adenoma, hepatic cyst, regenerative nodule of liver cirrhosis, and liver focal nodular hyperplasia [1, 2]. Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are two common types of primary liver cancer (PLC), and ICC may now account for roughly 10-15% of PLC cases [3, 4]. Relative to HCC, the epidemiology of ICC remains poorly understood, yet some risk factors have been suggested for ICC, such as congenital choledochal cyst, chronic cholangitis, primary sclerosing cholangitis, biliary cirrhosis, cholelithiasis, inflammatory bowel disease, parasitic infections, chemical carcinogens, liver cirrhosis, genetic factors, smoking, drinking, and alcoholic liver disease [4-7]. Our current report presents a case of primary intrahepatic bile duct adenocarcinoma complicating with nonalcoholic fatty liver disease, with no other risk factors found. In this report, we detail the case and discuss the risk factors in the context of literature.

## Case report

A 59-year-old Chinese female was referred to the Department of Gastroenterology, China-

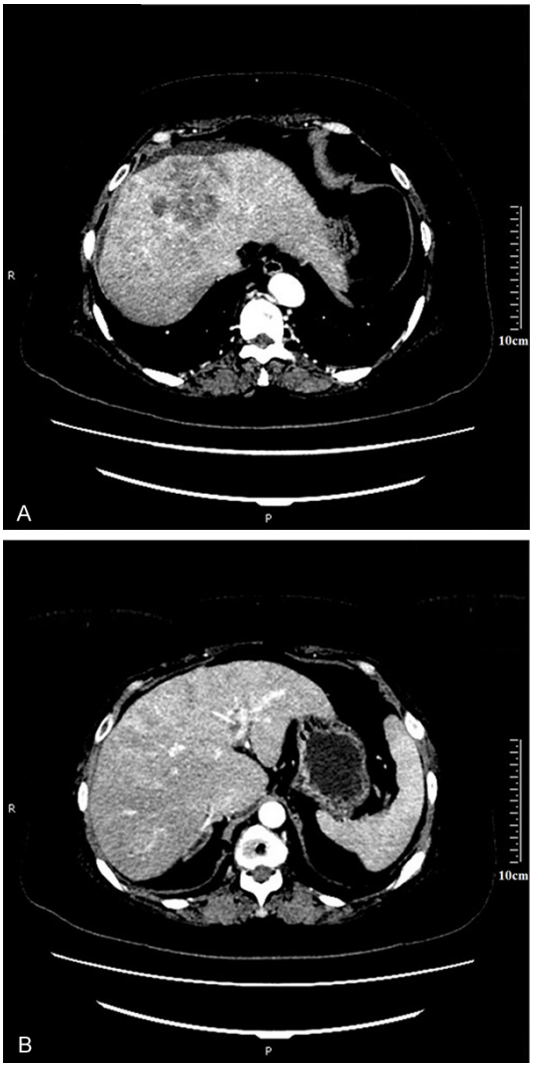


**Figure 1.** A. Abdominal enhanced computed tomography (CT) revealed multiple nodules and masses in the liver parenchyma and the largest was about 55 mm in diameter. B. Abdominal CT showed the typical imaging characteristics for fatty liver.

Japan Friendship Hospital, Ministry of Health (Beijing, China) on July 6, 2017 presenting with fatigue, anorexia, nausea and sour regurgitation for 6 months. About five months before admission, an upper gastrointestinal barium meal examination was performed, and no obviously abnormal findings were demonstrated. Two days earlier in the Section for Outpatients of our hospital, an abdominal ultrasonography (USG) was performed, which revealed multiple hypoechoic masses of different sizes in the liver, with the largest being a 73×50-mm mass located in the right lobe of the liver. Moreover, the typical sonographic appearances for severe fatty liver and chronic kidney disease were found in USG. In order to determine the property of the liver space-occupying lesions, this patient was admitted. All of the patient's data was collected with the approval of the institutional review board, and informed consent was obtained.

The patient had a medical history of fatty liver for 20 years, hypertension for 10 years and chronic kidney disease for less than one year. She strongly denied any history of other diseases, including viral hepatitis, diabetes mellitus, cardio-cerebrovascular disease, and other liver diseases. She was a non-smoker and had no history of alcohol intake, infective water contact, or blood transfusion. We asked her about intake of known toxins, drugs or dietary supplements, but she denied taking them. Her physical examination indicated that she was very obese, with a body weight of 92 kilograms (Body Mass Index, BMI, 32.86 $Kg/m^2$), although a decrease of 8Kg in weight in the preceeding two months was reported because of her discomfort. Her initial vital signs were as follows: body temperature, 36.6°C; heart rate, 88 beats/min; respiratory rate, 18 breaths/min; and blood pressure, 113/86 mmHg. Her abdomen was distended, and no other positive signs were found during the course of physical examination.

Laboratory investigations showed these results: alanine aminotransferase, 113 IU/L (normal range, NR, 0-40 IU/L); aspartate aminotransferase, 975 IU/L (NR, 0-42 IU/L); γ-glutamyl transpeptidase, 665 IU/L (NR, 0-52 IU/L); alkaline phosphatase, 289 IU/L (NR, 40-150 IU/L); albumin, 35 g/L (NR, 35-55 g/L); total bilirubin, 22.2 μmol/L (NR, 5.0-21.0 μmol/L); creatinine, 369.6 μmol/L (NR, 35-106 μmol/L); glucose, 3.98 mmol/L (NR, 3.61-6.11 mmol/L); triglyceride, 1.81 mmol/L (NR, <1.70 mmol/L); cholesterol, 4.66 mmol/L (NR, <5.20 mmol/L); alpha-fetoprotein (AFP), 3.16 ng/ml (NR, ≤7.00 ng/ml); carcinoembryonic antigen (CEA), 60.30 ng/ml (NR, <5.00 ng/ml); and carbohydrate antigen 19-9 (CA19-9), 98.58 U/ml (NR, <27.00 U/ml). The blood sample tested negative for all the antibodies for hepatitis B virus (HBV), HCV, HAV, HEV, cytomegalovirus (CMV) and Epstein-Barr virus (EBV). No abnormal findings were shown for thyroid function or the autoantibody spectrum of autoimmune diseases.

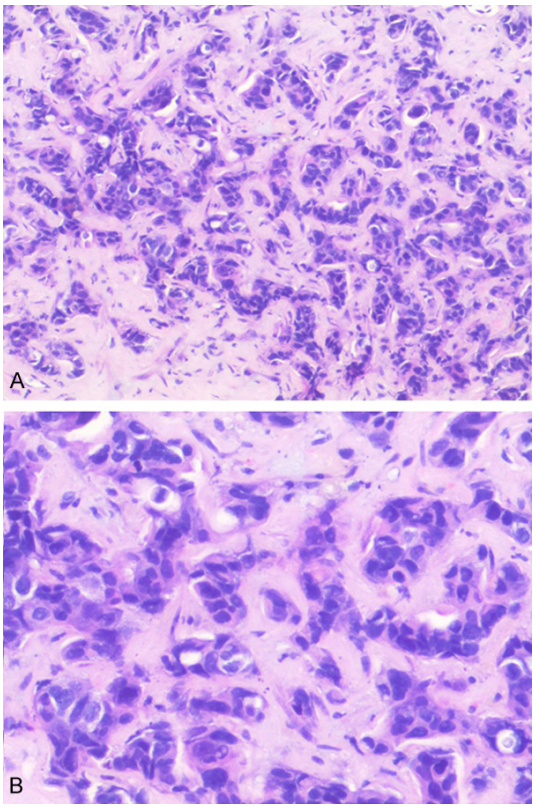


**Figure 2.** Pathological diagnosis indicated poorly differentiated adenocarcinoma (Hematoxylin-Eosin staining). A. Magnification (×10). B. Magnification (×20).

Abdominal enhanced computed tomography (CT) revealed multiple nodules and masses in the liver parenchyma, with the largest about 55 mm in diameter (**Figure 1A**). In addition, the typical imaging characteristics for severe fatty liver and a small amount of peritoneal effusion were found (**Figure 1B**). To determine the cause of liver space-occupying lesions, exclude metastatic liver cancer, and identify the potential site of the original tumor, some radiological and endoscopic examinations were performed, including gynecological ultrasound, chest CT, pelvic CT, cranial magnetic resonance imaging (MRI), esophagogastroduodenoscope, and colonoscopy. However, no abnormal findings were demonstrated, and no original tumor sites were found.

Considering that the diagnosis was not clear with these above-mentioned methods, an ultrasound-guided liver biopsy was performed under the premise of informed consent. Pathological diagnosis indicated poorly differentiated adenocarcinoma (**Figure 2**). Immunohistochemical staining was performed and the positive expression was detected for cytokeratin 7 (CK7), CK8/18 (**Figure 3**), CK19 (**Figure 4**), mammaglobin, estrogen receptor (ER/SP1), progesterone receptor (PR/1E2), glutamine synthetase (GS) and Ki67 (60%), whereas the negative expression was found for hepatocyte, alpha-fetoprotein (AFP), glypican-3 (GPC-3), Wilm's tumor protein 1 (WT-1), CK20, CD34, synaptophysin (Syn), chromogranin A (CgA), CD56, thyroid transcription factor-1 (TTF-1), NapsinA, caudal homeobox transcription factor-2 (CDX-2), gross cystic disease fluid protein 15 (GCDFP 15) and carbohydrate antigen 125 (CA125). Combined with pathological and immunohistochemical results, the primary intrahepatic bile duct adenocarcinoma for this patient was determined.

In the following ten days, her liver and renal functions rapidly failed, peritoneal effusion increased rapidly, and the patient eventually fell into a coma. On July 29, 2017, laboratory investigations showed that the total bilirubin was 284.72 μmol/L and creatinine was 704.3 μmol/L. She died on July 30, 2017.

## Discussion

Our current report detailed an eldly woman with multiple liver space-occupying lesions (SOLs). USG revealed multiple hypoechoic masses of different sizes in the liver, and an abdominal CT showed multiple nodules and masses in the liver parenchyma. Because those radiological and endoscopic examinations could not determine the diagnosis, an ultrasound-guided liver biopsy was performed. Pathological diagnosis indicated poorly differentiated adenocarcinoma. Immunohistochemical staining showed that the expression of CK7, CK8/18, CK19, mammaglobin, ER/SP1, PR/1E2 and GS were positive, whereas the expression of Hepatocyte, AFP, GPC-3, WT-1, CK20, CD34, Syn, CgA, CD56, TTF-1, NapsinA, CDX-2, GCDFP 15 and CA125 were negative. Combined with pathological and immunohistochemical results, the diagnosis for this patient was determined to be primary intrahepatic bile duct adenocarcinoma.

The SOLs of liver can be caused by varies of diseases, including malignant lesions, such as primary liver cancers and metastatic tumors,

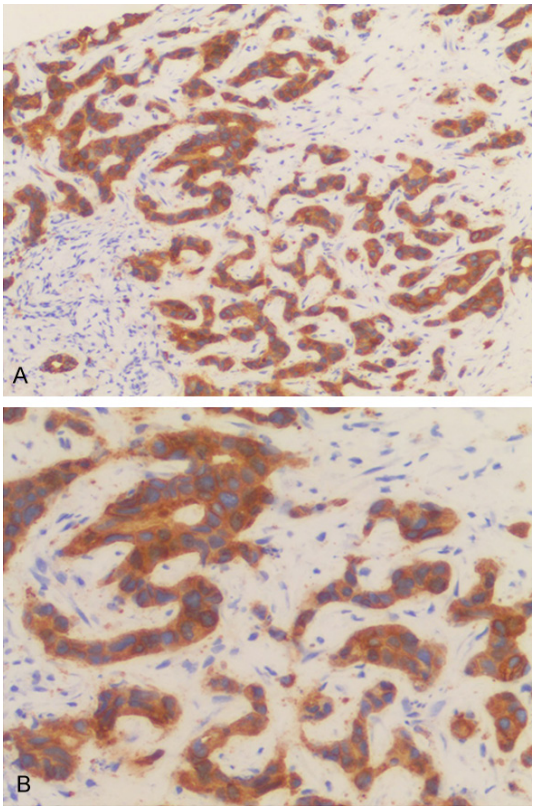


**Figure 3.** Immunohistochemical staining showed that the expression of CK8/18 was positive. A. Magnification (×10). B. Magnification (×20).

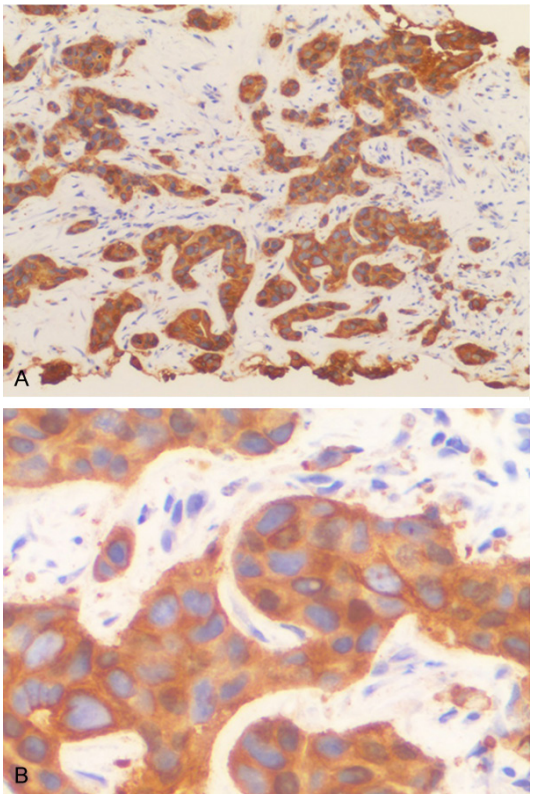


**Figure 4.** Immunohistochemical staining showed that the expression of CK19 was positive. A. Magnification (×10). B. Magnification (×40).

and benign lesions [1]. Of these lesions, primary liver cancer is less common than metastatic tumors, and bile duct cancer or carcinoma (cholangiocarcinoma) is very rare as has been-reported [1, 2]. One study included 101 adequate samples of patients with hepatic mass lesions and found that 100 were malignant and only one was benign (liver abscess) [1]. Of the 100 malignant lesions, 73 were metastatic adenocarcinomas, 8 were hepatocellular carcinomas, 1 was hepatoblastoma, and 18 were unclassified malignancies. Another study reviewed 32 pediatric liver SOLs and found 20 were malignant that included metastases (6), hepatocellular carcinoma (4), hepatoblastoma (7), and undifferentiated sarcoma (3) [2].

For this patient, under the impression of metastatic tumor or primary liver cancer, the elderly woman received many radiological and endoscopic examinations, and finally, an ultrasound-guided liver biopsy was performed. Combined with pathological and immunohistochemical results, the diagnosis was finally determined. As described in the Introduction, relative to HCC, the epidemiology of ICC or intrahepatic bile duct carcinoma remains unclear, but some risk factors have been suggested [4-7]. Based on her medical history and the results of laboratory investigations, radiological and endoscopic examinations, no definite risk factor was found for this woman. However, we found that the patient had a medical history of fatty liver for 20 years, she was obese and her body weight was 92 kilograms (BMI, 32.86 Kg/m$^2$). Abdominal USG and enhanced CT revealed the typical imaging characteristics for fatty liver. According to our current knowledge [8], nonalcoholic fatty liver disease may be a possible risk factor for this patient with intrahepatic bile duct adenocarcinoma.

Nonalcoholic fatty liver disease has been associated with ICC or intrahepatic bile duct adenocarcinoma [9, 10]. One study conducted in the University of Maryland School of Medicine (Baltimore, USA) included 181 patients with intrahepatic cholangiocarcinoma and found that 31 (17.1%) of them had underlying nonalcoholic steatohepatitis [9]. Moreover, the authors found that those patients with nonalco-

holic steatohepatitis had an increased incidence of macrovascular and any vascular tumor invasion. Another study conducted in Japan included 43 ICC patients without known risk factors for ICC [10]. They showed the association of dyslipidemia (DL) with the outcomes of hepatic resection in ICC patients.

Therefore, considering all these factors together, we deduce that nonalcoholic fatty liver disease may be the possible risk factor for this patient with intrahepatic bile duct adenocarcinoma, but a mere coincidence cannot be ruled out. For a better understanding of the relationship between ICC and nonalcoholic fatty liver disease, more studies are required, especially well-designed prospective studies.

## Disclosure of conflict of interest

None.

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